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ARTICLE

How large must a dose-optimization trial be?

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Abstract

Recently promulgated Draft Guidance from the US Food and Drug Administration Oncology Center of Excellence (OCE) recommends randomized, parallel dose–response trials for "dose optimization," but with vaguely stated aims that engage none of the statistical principles which typically attend randomization. Here, I advance a criterion for reasonable precision of such trials, and examine its implications for minimum enrollment, within a utility-based framework that acknowledges interindividual heterogeneity simultaneously in pharmacokinetics/pharmacodynamics and in the subjective evaluation of efficacy-toxicity trade-offs. Even when designed and conducted under ideal circumstances, reasonably sized trials of the kind advocated by OCE may need to enroll many hundreds of participants.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Under the rubric of "Project Optimus," the US Food and Drug Administration's Oncology Center of Excellence (OCE) has developed a doctrine that urges dose-randomization studies for "dose optimization" before conducting phase III registration trials of cancer drugs. Absent any formal analysis or simulation studies, it remains unclear how the OCE intends such trials to be designed or analyzed.

WHAT QUESTION DID THIS STUDY ADDRESS?

What criteria must a reasonable dose-randomization study meet? How many participants must these studies enroll to meet these criteria?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Dose-randomization studies require enrollments in the hundreds to properly characterize the efficacy-toxicity trade-offs between two doses, even assuming optimal foresight in choosing the dose pair tested.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The formal model proposed here may help designers of oncology clinical trials to think more concretely and realistically about interindividual heterogeneity in dose-efficacy trade-offs.

INTRODUCTION

The US Food and Drug Administration (FDA) Oncology Center of Excellence (OCE) has recently promulgated draft guidance recommending randomized, parallel dose–response trials for "dose optimization,"[1] apparently without having undertaken formal modeling and simulation work to sharpen their thinking.[2–4] Principles of pharmacometrics can be useful not only in the analysis of preclinical and early-phase trial data, but also for abstract foundational concept development as needed for the rational development of such guidance.

METHODS

A model of individual-patient efficacy-toxicity trade-off is posited, with heterogeneity across individuals regarding both dose-efficacy and dose-toxicity relations. The model is solved to obtain a closed-form expression for individually optimal dosing, and numerical methods are used to find the "optimal [single] dose" that maximizes expected utility in the population under one-size-fits-all dosing. The ratio of benefit to harm terms in this expected utility is proposed as a measure of intrinsic drug tolerability. An expression for the utility lost to the one-size-fits-all dosing constraint is also given. Finally, a criterion is proposed for reasonable precision of a dose-randomization trial, then a formula for the minimum size of such a trial is derived and explored numerically as a function of drug tolerability and interindividual variability of pharmacokinetics and pharmacodynamics (PK/PD). All computation was done with Julia version 1.9.[5]

Utilities

We take therapeutic efficacy, measured as the probability of achieving some good outcome, such as a remission, to constitute a utility measure. We posit a maximum effect (E_{max})-type dose-efficacy curve:

$$\begin{aligned} P_r(D) &= \mathrm{P}_{\max}\left(1-0.5^{D/\mathrm{ED}_{50}}\right) \\ &= \mathrm{P}_{\max}\left[1-\exp\left(-\frac{D\ln 2}{\mathrm{ED}_{50}}\right)\right], \quad 0<\mathrm{P}_{\max}\le 1, \end{aligned} \tag{1}$$

monotone increasing and concave, with $P_r\left(\mathrm{ED}_{50}\right) \equiv 0.5\,\mathrm{P}_{\max}$ and asymptote $P_r(\infty) = \mathrm{P}_{\max}$.

We will suppose that the disutility of toxicity T can be expressed objectively in units of P_r, and that the dose-toxicity relation $T(D)$ is of the convex form:

$$T(D) = \left(\frac{D}{D^*}\right)^{1+\eta}, \quad \eta > 0. \tag{2}$$

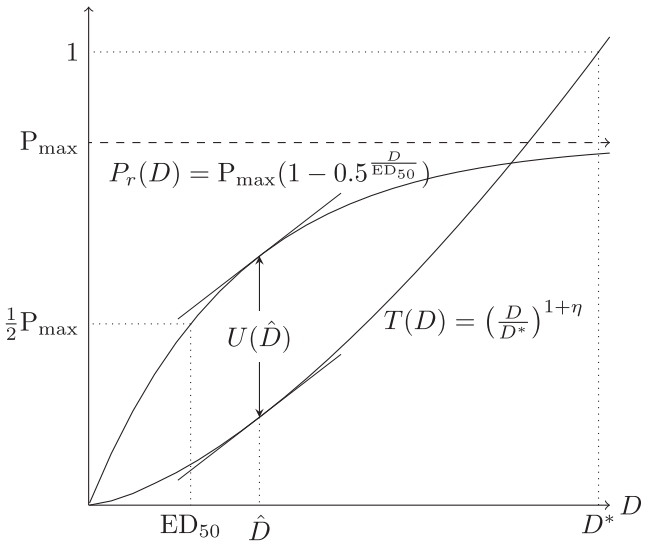

FIGURE 1 The individual-level dose-optimization problem of Equations 1–3.

Note that $T(D^*) \equiv 1$ means the toxicity at dose D^* is severe enough to nullify even the maximal utility $P_r = 1$ of certain therapeutic benefit. Thus D^* sets a strict upper bound on the tolerable dose range. While adopting the simplifying assumption that η is a fixed characteristic of the therapy itself, we will suppose D^* varies from one patient to another to reflect heterogeneity jointly in individuals' PK/PD and in their subjective evaluation of toxicity.

Individually optimal dosing

As depicted in Figure 1, the net utility $U(D) = P_r(D) - T(D)$ is then strictly concave, and its unique maximum occurs at the (individually) optimal dose $\hat{D}$ determined by:

$$P_r'\left(\hat{D}\right) = T'\left(\hat{D}\right). \tag{3}$$

It is relatively straightforward to transform Equation 3 to:

$$\left(\frac{\eta\,\mathrm{P}_{\max}}{1+\eta}\right)^{1/\eta}\left(\frac{D^*\ln 2}{\eta\,\mathrm{ED}_{50}}\right)^{\frac{1+\eta}{\eta}} = \frac{D\ln 2}{\eta\,\mathrm{ED}_{50}}\exp\left(\frac{D\ln 2}{\eta\,\mathrm{ED}_{50}}\right),$$

which we may see has the form $z = we^w$, if we identify its left-hand side with z and $D\ln 2 / \left(\eta \mathrm{ED}_{50}\right)$ with w. Because $z > 0$, this has the unique real solution $w = W_0(z)$, where W_0 denotes the principal branch of the Lambert W function.[6,§4.13] Thus we obtain:

$$\hat{D}\left(\mathrm{ED}_{50}, D^*\right) = \frac{\eta\,\mathrm{ED}_{50}}{\ln 2}\; W_0\left[\left(\frac{\eta\,\mathrm{P}_{\max}}{1+\eta}\right)^{\frac{1}{\eta}}\left(\frac{D^*\ln 2}{\eta\,\mathrm{ED}_{50}}\right)^{\frac{1+\eta}{\eta}}\right]. \tag{4}$$

Expected utilities

To develop population-average results, we will suppose that the parameters $\mathrm{P}_{\max}$ and η are fixed, whereas ED_{50} and D^* are inverse-gamma distributed:

$$\mathrm{ED}_{50} \sim \text{Inv-Gamma}(\alpha, \beta)$$
$$D^* \sim \text{Inv-Gamma}(a, b),$$

the Inv-Gamma density being:

$$f(x;\alpha,\beta) = \frac{\beta^\alpha}{\Gamma(\alpha)} x^{-\alpha-1}\exp(-\beta/x).$$

The closed form of Equation 4 enables us efficiently to compute the integrand in:

$$E\left[U\left(\widehat{D}\right)\right] = \int_0^\infty \int_0^\infty U\left(\widehat{D}(x,y)\right) f(x;\alpha,\beta) f(y;a,b)\,\mathrm{d}x\,\mathrm{d}y, \quad (5)$$

to integrate numerically for the expected (per capita) utility of individually optimal dosing. The integrals in the expected utility $\overline{U}(D) = \overline{P}_r(D) - \overline{T}(D)$ of a one-size-fits-all dose D, however, are readily obtained in closed form:

$$\begin{aligned}\frac{\overline{P}_r(D)}{\mathrm{P}_{\max}} &= \int_0^\infty \left[1-\exp\left(-\frac{D\ln 2}{x}\right)\right]\frac{\beta^\alpha}{\Gamma(\alpha)}x^{-\alpha-1}\exp\left(-\frac{\beta}{x}\right)\mathrm{d}x \\ &= 1-\int_0^\infty \frac{\beta^\alpha}{\Gamma(\alpha)}x^{-\alpha-1}\exp\left(-\frac{\beta}{x}-\frac{D\ln 2}{x}\right)\mathrm{d}x \\ &= 1-\left(\frac{\beta}{\beta+D\ln 2}\right)^\alpha \int_0^\infty f(x;\alpha,\beta+D\ln 2)\,\mathrm{d}x \\ &= 1-\left(\frac{\beta}{\beta+D\ln 2}\right)^\alpha = 1-\left(1+\frac{\ln 2}{\beta}D\right)^{-\alpha}\end{aligned} \quad (6)$$

and

$$\begin{aligned}\overline{T}(D) &= \int_0^\infty \left(\frac{D}{x}\right)^{1+\eta}\frac{b^a}{\Gamma(a)}x^{-a-1}\exp\left(-\frac{b}{x}\right)\mathrm{d}x \\ &= \frac{D^{1+\eta}\Gamma(a+1+\eta)}{b^{1+\eta}\Gamma(a)}\int_0^\infty f(x;a+1+\eta,b)\,\mathrm{d}x \\ &= \frac{\Gamma(a+1+\eta)}{\Gamma(a)}\left(\frac{D}{b}\right)^{1+\eta}.\end{aligned} \quad (7)$$

A quantity of particular interest is the ratio:

$$\tau(D) = \frac{\overline{P}_r(D)}{\overline{T}(D)} = \frac{\mathrm{P}_{\max}\left[1-\left(1+\frac{\ln 2}{\beta}D\right)^{-\alpha}\right]}{\frac{\Gamma(a+1+\eta)}{\Gamma(a)}\left(\frac{D}{b}\right)^{1+\eta}}, \quad (8)$$

interpretable as a *tolerability index* for dose D: large values $\tau(D) \gg 1$ indicate that benefit $\overline{P}_r(D)$ far outweighs harms from toxicity $\overline{T}(D)$, whereas values of $\tau(D)$ approaching 1 indicate that harms nearly cancel out benefits; $\tau(D) < 1$ indicates net harm at dose D.

It is especially noteworthy that Equation 7 may be written as:

$$\overline{T}(D) = \overline{T}(1)\cdot D^{1+\eta} = \frac{\overline{P}_r(1)}{\tau(1)}D^{1+\eta}, \quad (9)$$

showing that $\overline{T}(D)$ depends on parameters a and b only through $\tau(1)$. This proves to be important below, where by normalizing our dose units so that median $\mathrm{ED}_{50} \equiv 1$, we render $\tau(1)$ interpretable as the tolerability of median ED_{50}.

Optimal one-size-fits-all dosing

A regulatory agency constrained to "advocating a [single] dose for a population"[7, at [1:08:07]] faces the problem of finding the population-optimal dose:

$$\tilde{D} = \arg\max_D \overline{U}(D). \quad (10)$$

Being a straightforward population-average over many optimization problems such as depicted in Figure 1, this problem possesses the same concavity, and enjoys the same guarantee of a unique positive solution, which we obtain by solving a first-order condition analogous to Equation 3:

$$\begin{aligned}\overline{P}_r'(\tilde{D}) &= \overline{T}'(\tilde{D}) \\ \alpha\,\mathrm{P}_{\max}\left(1+\frac{\ln 2}{\beta}\tilde{D}\right)^{-\alpha-1}\left(\frac{\ln 2}{\beta}\right) &= \frac{\overline{P}_r(1)}{\tau(1)}(1+\eta)\tilde{D}^\eta \\ \frac{\alpha}{1+\eta}\frac{\mathrm{P}_{\max}\tau(1)}{\overline{P}_r(1)}\left(\frac{\ln 2}{\beta}\right)^{1+\eta} &= \left(\frac{\ln 2}{\beta}\tilde{D}\right)^\eta\left(1+\frac{\ln 2}{\beta}\tilde{D}\right)^{\alpha+1} \\ \frac{\alpha}{1+\eta}\frac{\tau(1)}{\left[1-\left(1+\frac{\ln 2}{\beta}\right)^{-\alpha}\right]}\left(\frac{\ln 2}{\beta}\right)^{1+\eta} &= \left(\frac{\ln 2}{\beta}\tilde{D}\right)^\eta\left(1+\frac{\ln 2}{\beta}\tilde{D}\right)^{\alpha+1}.\end{aligned}$$

This takes the form:

$$C = x^\eta(1+x)^{\alpha+1}, \quad x = \frac{\ln 2}{\beta}\tilde{D},$$

which we solve for $\tilde{D} = \beta x/\ln 2$ by finding the unique real root of:

$$\eta\ln x + (1+\alpha)\ln(1+x) - \ln C = 0. \quad (11)$$

Section S1 develops bounds for a numerical search.

Whereas I have previously treated the cost of one-size-fits-all dosing solely in terms of its impact on efficacy,[8,9] Equations 5, 6, 7, and 10 allow for a more coherent and comprehensive treatment of net utility loss:

$$E\left[U\left(\widehat{D}\right)\right] - \overline{U}(\tilde{D}). \quad (12)$$

For further exploration of this, see Section S2.

A lower bound on dose-randomization trial size

Although generally dose optimization may require adaptive exploration that ranges over many distinct doses, in order to obtain a strong lower bound on dose-randomization trial size, we consider the power-maximizing limit where n participants are randomized to one of two doses.

Suppose we enroll a total of n participants into two arms each of size $n/2$, at doses $D_1 < D_2$ with respective efficacy probabilities $p_1 < p_2$; then the observed difference in proportions of successes in the two arms is an unbiased estimator of $p_2 - p_1$ with standard error:

$$\sigma_{\widehat{p_2-p_1}} = \sqrt{\frac{p_1(1-p_1)}{n/2} + \frac{p_2(1-p_2)}{n/2}}. \tag{13}$$

Adopting the rather weak standard that properly characterizing the difference $p_2 - p_1$ requires that Equation 13 not exceed half the actual difference $p_2 - p_1$, then we obtain the bound:

$$n \geq 8\frac{p_1(1-p_1) + p_2(1-p_2)}{(p_2-p_1)^2}. \tag{14}$$

To obtain a definite bound, we furthermore apply this criterion to a trial ideally designed to exhibit the canonical aspiration of Project Optimus: one in which the lower dose just so happens to be $\tilde{D}$, and the higher dose imposes twice the toxicity burden of the lower dose:

$$D_1 = \tilde{D}, \quad E\left[T(D_2)\right] = 2 \cdot E\left[T(D_1)\right]. \tag{15}$$

Happily, the simple power-law form of $T(D)$ (see also Equation 9) allows us to solve Equation 15 for D_2 in terms of D_1: $D_2 = D_1 \cdot 2^{1/(1+\eta)}$. Thus, we may obtain a definite lower bound on n by substituting:

$$p_1 = \overline{P}_r(\tilde{D}), \quad p_2 = \overline{P}_r\left(\tilde{D} \cdot 2^{1/(1+\eta)}\right) \tag{16}$$

on the RHS of Equation 14:

$$n_{\min} = 8\frac{p_1(1-p_1) + p_2(1-p_2)}{(p_2-p_1)^2}\Bigg|_{p_1=\overline{P}_r(\tilde{D}),\ p_2=\overline{P}_r(\tilde{D}\cdot 2^{1/(1+\eta)})}. \tag{17}$$

This trial is depicted in Figure 2, the purely geometrical nature of which abstracts away the dose scale, thereby underscoring the genericity of our analysis. (The specific dimensions shown incidentally match the worked example in Section S3.)

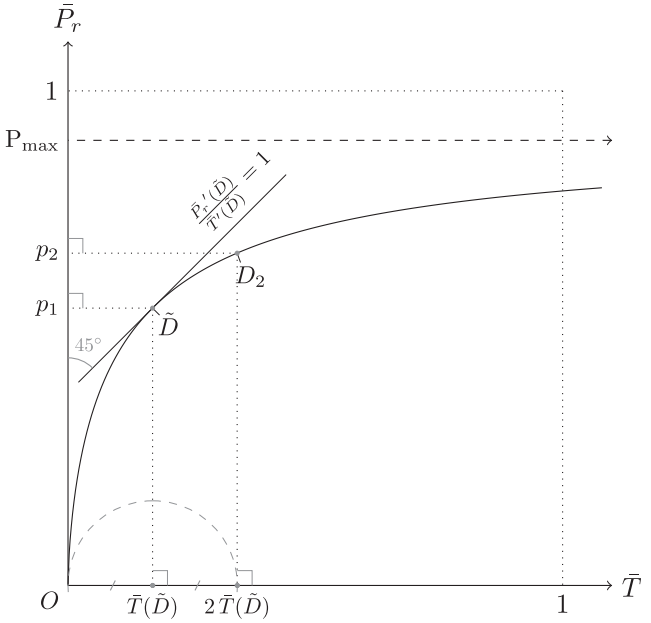

FIGURE 2 The dose-optimization trial of Equations 10, 15, and 16, depicted as a geometrical construction upon the graph of the D-parametrized curve $(\overline{T}, \overline{P}_r)(D)$. The optimal one-size-fits-all dose $\tilde{D}$ is easily located with a 45/90° drafting triangle, at the point where a tangent to this curve has slope 1. The twice-as-toxic dose D_2 may be constructed by projecting $\tilde{D}$ down to $\overline{T}(\tilde{D})$ on the horizontal axis, doubling this with the compass, and projecting $2\overline{T}(\tilde{D})$ back up to the curve. By projecting these two doses onto the vertical axis, we obtain their efficacy probabilities p_1 and p_2.

A systematic reduction of the parameter space

The model posited here involves no fewer than 6 distinct parameters: $\{P_{max}, \alpha, \beta, \eta, a, b\}$. The β dimension may be eliminated by scaling dose units so that median ED_{50} is 1. Furthermore, because parameters a and b enter into Equation 17 only via $\tilde{D}$'s dependence on $\tau(1)$, we can collapse the two dimensions (a, b) to the single dimension of $\tau(1)$ in an analysis of $n_{\min}$. (Importantly, our scaling of dose units renders $\tau(1)$ readily interpretable, as the tolerability of median ED_{50}.) Of the four dimensions that remain after these reductions, we condition on a few discrete values of P_{max} and η:

$$(P_{max}, \eta) \in \{0.8, 0.9, 1\} \times \left\{0.1, \frac{1}{2}, 1\right\}, \tag{18}$$

then use two-dimensional contour plots to describe the remaining dependence of $n_{\min}$.

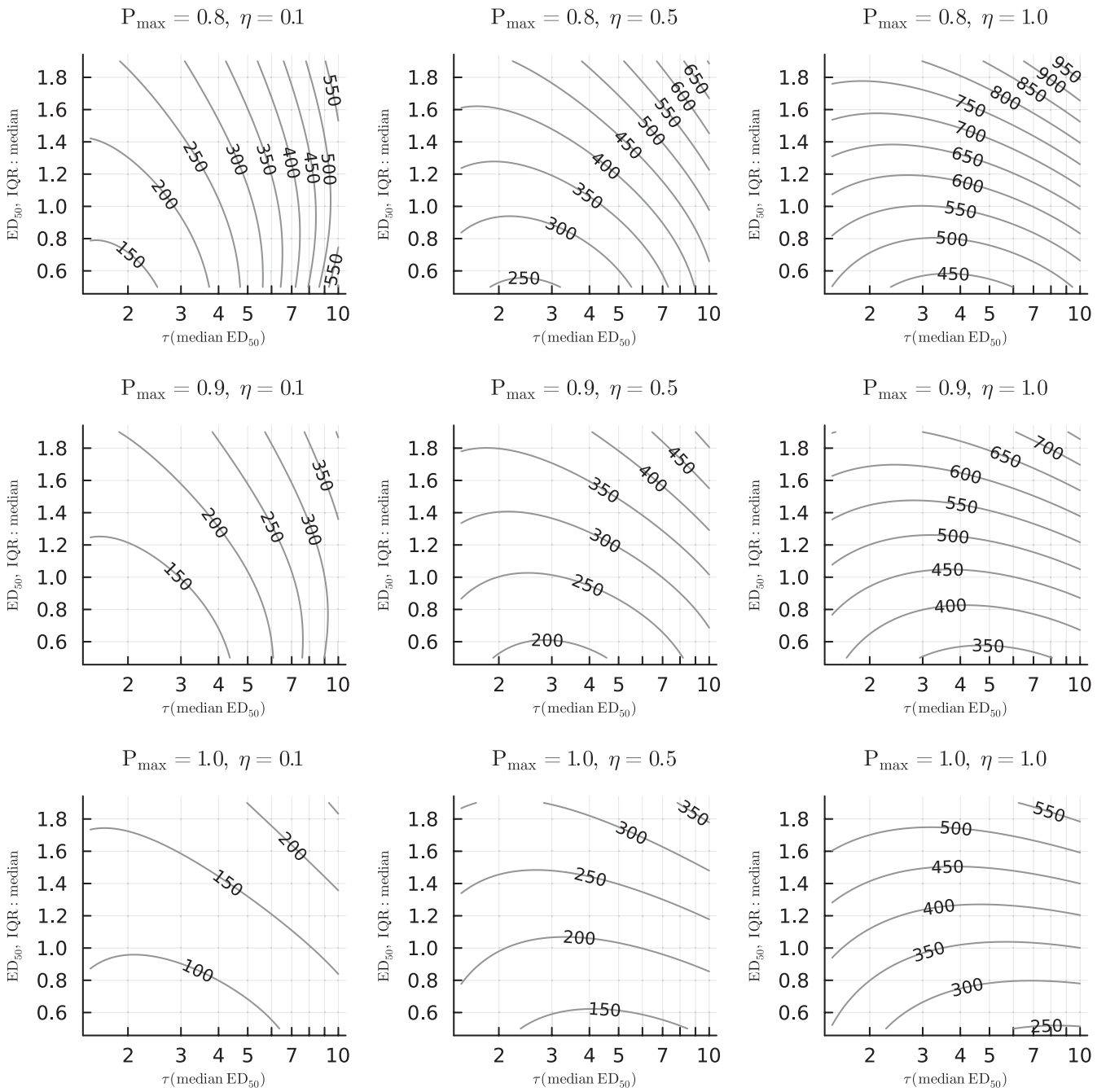

FIGURE 3 Minimum enrollment for dose-randomization trials, according to Equations 10, 14, and 16 as a function of drug tolerability and interindividual variability (IIV) in ED_{50}, under several possible combinations of (P_{max}, η). The tolerability index τ of Equation 8 is evaluated at median ED_{50}, and shown on a logarithmic scale. The ratio of interquartile range (IQR) to median is used to quantify IIV of ED_{50}.

RESULTS

Our key result is shown in Figure 3, where level curves of n_{min} are plotted in the plane determined by plausible ranges for $\tau(\text{median } ED_{50})$ and $\frac{IQR}{median}(ED_{50})$, for several discrete values of P_{max} and η. Dose-randomization trials meeting our reasonableness criterion (Equations 14 and 15) generally require enrollment of at least several hundred participants. Although some corner regions in Figure 3 agree in magnitude with sizes of randomized dose-optimization trials OCE cites as exemplary (e.g., $N = 196$ for DREAMM-2),[3] it is notable that even modest departures from $P_{max} = 1$ inflate n_{min} well above 200—especially for the intrinsically more tolerable drugs ($\tau \gg 2$) specifically cited in the rationale of Project Optimus. Indeed, Figure 2 offers some geometrical intuition for how decreasing P_{max} may crowd p_1 and p_2 closer together, shrinking the denominator of Equation 17 and driving n_{min} higher.

DISCUSSION

To my knowledge, the design of oncology dose-optimization trials has not previously been explored in a setting that explicitly acknowledges continuous variability between patients in respect to their PK/PD and to the utilities underlying their consideration of efficacy-toxicity trade-offs. I have previously analyzed the safety of dose-finding trials as a function of PK/PD heterogeneity.[10,11] Heterogeneity over utilities has been considered previously in a categorical manner, linked to predefined prognostic subgroups.[12,13]

Explicit acknowledgment of continuous variation in PK/PD tends to raise the specter of adaptive dose individualization,[14–16] which the FDA's OCE shuns because:

> That is what an individual doctor has to do with an individual patient, and here again, that doesn't kind of fit in to the FDA because we're advocating a dose for a population. But ... for an individual [dosing] decision, that is the practice of medicine that the FDA does not regulate.[7, at [1:07:53]]

One need not appeal to regulatory politics, however, to conceive circumstances in which dose-randomization trials of the kind analyzed here might rationally be undertaken. If treatment occurs in a relatively brief episode, for example, so that neither benefits nor toxicities become evident until after administration of a full dose, then the modality offers no reasonable prospect for dose titration. (The hypothetical case of a single radiation treatment might be taken to exemplify this situation.) Such a setting also averts troublesome factors, such as treatment discontinuation, that would complicate the simple trial analysis presumed in Equation 13. It is clear, however, that the FDA OCE intends that dose-randomization trials be undertaken quite broadly, with indeed much emphasis being placed on modern targeted agents that are intrinsically more tolerable than chemotherapy, and may be administered chronically.[1–3] Nevertheless, because of the manner in which it concedes optimal foresight in trial design and conduct, the analysis offered here applies to any one-size-fits-all "dose optimization" trial, whether its rationale be political or driven by essential characteristics of the therapy.

Regarding the particular question addressed here, namely that of trial sample sizes, the new Draft Guidance states:

> The trial should be sized to allow for sufficient assessment of activity, safety, and tolerability for each dosage. The trial does not need to be powered to demonstrate statistical superiority of a dosage or statistical non-inferiority among the dosages.[1]

This echoes similar language from an antecedent *New England Journal of Medicine* Perspective:

> Although conducting noninferiority comparisons is probably infeasible in many small, biomarker-defined subgroups of patients with cancer, early efficacy, safety, and exposure-response data collected from a randomized trial would support more informed dose selection.[2]

The "reasonableness" criterion advanced here (Equations 14 and 15) aims to supply a rigorous basis for objective analysis, against the invitation to impressionistic judgment[4] offered by the vague language "sufficient assessment" and "more informed dose selection." We note that this criterion addresses directly "the major issue" motivating Project Optimus:

> It is very hard to retrofit a dose of the drug and I can't emphasize [enough] how important it is to try — and that's why we're spending all this time — to try to get it right up front, because: here again, you don't know then if, when you reduce a dose, will it have the same efficacy, and that's the major issue here.[7, at [1:08:18]]

The purely geometrical character of Figure 2 underscores the genericity of this criterion, and of the minimum trial sizes it implies.

But apart from this overt focus on trial size, the basic tools developed here may prove more broadly useful. For example, the objective *tolerability* notion expressed by τ may support rational comparisons of drug candidates in early development. The utility-based optimization framework of Equations 1, 2 and 10 may stimulate empirical research on the efficacy-toxicity trade-off considerations of real patients. Whether $0.1 < \eta < 1.0$ covers a relevant range of patient perspectives, and indeed whether Equation 2 suitably expresses a utility commensurable with Equation 1, are hardly obvious and warrant empirical scrutiny. My greatest hope for this analysis is that it demonstrates the possibility of formalizing pharmacologic notions underlying dose–response investigations, and provokes a critical response that generates further progress in that direction.

AUTHOR CONTRIBUTIONS

D.C.N. designed and performed the research, analyzed the data, and wrote the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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